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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/534,717	03/24/2000	JOCHEN SALFELD	BBI-093CP	2605

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EXAMINER
HAMUD, FOZIA M

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

File copy

Office Action Summary

Application No.	Applicant(s)
09/534,717	SALFELD et al
Examiner	**Art Unit**
Fozia Hamud	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 12, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-141* is/are pending in the application.

4a) Of the above, claim(s) *15-40, 50-62, 64-73, 75, 84-86, and 94-141* is/are withdrawn from consideration.

5) ☒ Claim(s) *41-49* is/are allowable.

6) ☒ Claim(s) *1-14, 63, 74, 76-83, and 87-93* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicants' election of the invention of Group I in Paper No. 9, filed on 29 August 2002 and Applicants' election of the species corresponding to SEQ ID Nos: 25-32 for to CDR1, CDR2 ans CDR3 regions and the therapeutic composition of antibodies or agonist of TNF, filed on 12 February 2003 in Paper No: 16 are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-14, 41-49, 63, 74-83 and 87-93 read upon elected species.

The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 15-40, 50-62, 64-73, 75, 84-86, 94-141 are withdrawn from consideration by the Examiner as they are drawn to non-elected inventions.

Specification

2. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim rejections-35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 2-14, 63, 74, 76-83, 87-93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated human antibody that has a heavy chain CDR3 which comprises the amino acid sequence set forth in SEQ ID NO:25, a light chain CDR3 which comprises the amino acid sequence set forth in SEQ ID NO:26, said antibody which further has a heavy chain and a light chain CDR2 comprising the amino acid sequences set forth in SEQ ID NO:27 and SEQ ID NO:28, respectively, said antibody which further has a heavy chain and a light chain CDR1 which comprises the amino acid sequence of SEQ ID NO:29 and SEQ ID NO:30, receptively, said antibody which further has a heavy chain variable region which comprises the amino acid sequence of SEQ ID NO:31, a light chain variable region which comprises the amino acid sequence set forth in SEQ ID NO:32, said antibody having the specific properties recited in claims 9-14 and 87, does not reasonably provide enablement for "all" selectively mutated human IL-12 antibodies or a therapeutic composition comprising human antibody that binds to human IL-12 which further comprises any of the agents recited in claims 91-93, or "all",possible antibodies that have amino acid selected from a VH3 Germaine family, or a light Vλ1 Germaine family, or which comprises a COS-3 Germaine amino acid sequence, or mutants thereof, with enhanced activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Instant claims 2-14 are drawn to a selectively mutated human IL-12, mutated at more than preferred one, two or three selective mutagenesis, which when mutated a target specificity is attained and at least one desirable property is attained. These claims encompass "all" possible selectively mutated human antibodies that bind to human IL-12, however, instant specification describes a

specific antibody that has specific mutations, said antibody is referred to as J695 and has mutations and properties disclosed on page 44, lines 15-37 of the instant specification. Therefore, instant specification is not enabling for "all" possible selectively mutated human antibodies that bind to human IL-12, as recited in claims 2-14, because the claims do not recite structural limitations for the claimed antibody. The claims recite "selectively mutated at one, two or three selective sites with enhance activity", however, there is no guidance as to where these selective mutations should take place. The claims recite functional limitations for the claimed antibody in the absence of clear and definite structural limitations. Instant specification is also non-enabling for the mutants recited in claim 63, because there is no guidance as to how many amino acids to substitute to achieve "a K_{off} rate no more than 10 fold". The specification demonstrates that the J695 antibody which comprises the specific structure recited in claims 41-44, inhibits PHA blast proliferation and has an improved neutralization activity, (see page 125, line 1-30). With respect to claims 91-93, support for a pharmaceutical composition is provided in the specification on page 91, line 33 through page 92 line 96 line 15, wherein it is disclosed that the claimed antibody can be used in combination with a therapeutic agent and where a multitude of disparate therapeutic agents are listed. However, no disclosure, beyond the mere mention of therapeutic agents is made in the specification. Instant specification does not disclose a specific case where the agents recited in claims 90-93 are used in combination with the claimed antibody. With respect to claims 74 and 76 instant specification is non enabling for "all" possible antibodies that have amino acids selected from a VH3 Germaine family, or a light Vλ1 from a Germaine family, or which comprises a COS-3 Germaine amino acid sequence, or mutants thereof with enhanced activity. With respect to claim 87, instant specification

is only enabling for the J695 antibody which neutralizes the activity of the human IL-12 and is non-enabling for an antibody that neutralizes human IL-12 with any one of the IL-12 proteins recited in the claim, because the specification does not demonstrate that the disclosed antibody neutralizes anything but human IL-12.

The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant application, it will be undue experimentation to make "all" possible mutant human antibodies that bind to human IL-12, because instant specification only discloses one specific antibody that has specific structural and functional properties and does not give guidance as to how to selectively mutate all others. Neither does the specification provide guidance as to which amino acids are essential for the biological activity and structural integrity and which residues are either expendable or substitutable. In the absence of this information a practitioner would have to resort to a substantial amount of undue experimentation to make a selectively mutated antibody with desirable properties. The only antibody enabled in the instant disclosure is the J695 antibody which has specific structural and functional properties. Furthermore, the state of the art is such that amino acid modifications of proteins is unpredictable, thus one of ordinary skill in the art would not be able to predict which mutations to J695 antibody, would result in a mutant which has a K_{off} rate no more

than 10 fold. Therefore, the quantity of experimentation to determine "all" possible selectively mutated human antibodies that bind to human IL-12, that are encompassed by the instant claims, are practically infinite and the guidance provided in the specification very little. Absent further guidance from the specification it would constitute undue experimentation to make the antibody recited in claims 2-14, 63, 74, 77-83, 87-93 as such these claims are not commensurate in scope with the specification but rather are much broader than the supporting disclosure.

3b. Claims 2-14, 63, 74, 77-83, 87-93 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only discloses an isolated human antibody that has a heavy chain CDR3 which comprises the amino acid sequence set forth in SEQ ID NO:25, a light chain CDR3 which comprises the amino acid sequence set forth in SEQ ID NO:26, said antibody which further has a heavy chain CDR2 which comprises the amino acid sequence of SEQ ID NO:27, a light chain CDR2 which comprises the amino acid sequence set forth in SEQ ID NO:28, said antibody which further has a heavy chain CDR1 which comprises the amino acid sequence of SEQ ID NO:29, a light chain CDR1 which comprises the amino acid sequence set forth in SEQ ID NO:30, said antibody which further has a heavy chain variable region which comprises the amino acid sequence of SEQ ID NO:31, a light chain variable region which comprises the amino acid sequence set forth in SEQ ID NO:32 and is not commensurate in scope with the claims drawn to "all' possible human antibodies that bind to IL-12 and mutants thereof. Instant specification also fails to describe

a pharmaceutical composition comprising an isolated human antibody that binds to human IL-12 and a therapeutic agent as recited in claims 90-93. Support for a pharmaceutical composition is provided in the specification on page 91, line 33 through page 92 line 96 line 15, wherein it is disclosed that the claimed antibody can be used in combination with a therapeutic agent and where a multitude of disparate therapeutic agents are recited. However, no disclosure, beyond the mere mention of therapeutic agents is made in the specification. With respect to claims 74 and 76 instant specification does not disclose the structures of "all" possible antibodies that have amino acid selected from a VH3 Germaine family, or a light Vλ1 from a Germaine family, or which comprises a COS-3 Germaine amino acid sequence, or mutants thereof with enhanced activity.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Instant specification only defines the structure of the J695 antibody with the specific structure and functional limitations recited in claims 41-44, and does not describe the structure of any other antibody that binds to IL-12 or a mutant thereof. Applicants have not described the structure of an antibody that is selectively mutated at one, two or three positions that has an enhanced activity. With the exception the isolated antibody that has the specific structure as set forth above, the skilled artisan cannot envision the detailed structure of the all encompassed antibodies and mutants,

therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of making it.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Therefore only an isolated human antibody that has a heavy chain CDR3 which comprises the amino acid sequence set forth in SEQ ID NO:25, a light chain CDR3 which comprises the amino acid sequence set forth in SEQ ID NO:26, said antibody which further has a heavy chain CDR2 which comprises the amino acid sequence of SEQ ID NO:27, a light chain CDR2 which comprises the amino acid sequence set forth in SEQ ID NO:28, said antibody which further has a heavy chain CDR1 which comprises the amino acid sequence of SEQ ID NO:29, a light chain CDR1 which comprises the amino acid sequence set forth in SEQ ID NO:30, said antibody which further has a heavy chain variable region which comprises the amino acid sequence of SEQ ID NO:31, a light chain variable region which comprises the amino acid sequence set forth in SEQ ID NO:32.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2-14, 63, 74, 76-83, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claims 2-14, 74, 76-83 and 87 are vague and indefinite because the claims recite "... .mutated at preferred selective mutagenesis or hyper mutation positions....with an activity enhancing amino acid residue .....at more than preferred one, two or three selective mutagenesis...", however, it is unclear where those hyper mutation positions are, and which amino acid residues are activity enhancing residues. Furthermore, the metes and bounds of the claims can not be ascertained, because it is unclear how many positions to mutate. These claims also recite, the phrase "such that" which renders them indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). It is also unclear as to how many selective sites should be mutated. Claim 8 recites "....further retains at least one desirable property or characteristic", however, it is unclear which characteristic or property is being refereed to. Claim 7 recites "..... ~~which when~~ is selectively such that mutated *a target specificity* affinity level is attained...", however, it is unclear what this phrase means. Appropriate correction is required.

4b. Claim 63 is rejected under 35 U.S.C. 112, second paragraph, because the claim recites "....one or more amino acid substitutions...", which renders the claim vague and indefinite, because it is unclear how many amino acids to substitute. Appropriate correction is required.

4c. Claim 87 recites "an isolated human antibody ....., that selectively neutralizes the activity of human IL-12 and at least one additional primate IL-12....", however, it is unclear whether the claimed antibody neutralizes the combined activities of the human IL-12 and marmoset Il-12 for example, or whether it neutralizes the activity of the human IL-12 and also the activity of the other IL-12 proteins recited in the claim. Appropriate correction is required.

Claim rejections-35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> > (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Trinchieri et al (U.S. Patent 5,811,523).

Trinchieri et al disclose a human antibody which specifically binds to human natural killer cell stimulatory factor (also known as IL-12) , (column 2, line 1-23 and claims). The antibody disclosed by Trinchieri et al neutralizes the activity of human IL-12. Therefore, the Trinchieri et al reference clearly anticipates instant claim 1.

Conclusion

6. Claims 41-49 are allowable.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8891. The examiner can normally be reached on Monday-Thursdays from 7:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit 1647
18 March 2003

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER